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# **S-100 protein expression of spindle cells in spindle cell lipoma: a diagnostic pitfall**

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**Short running title: S-100 positive spindle cell lipoma**

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## **2Abstract:**

Spindle cell lipoma represents a distinct clinicopathological entity and is related to cellular angiofibroma and mammary-type myofibroblastoma. Cases of spindle cell lipoma are composed of mature lipogenic cells and a variable number of CD34-positive spindle cells that show loss of retinoblastoma protein expression. Spindle cell lipoma may rarely express S-100 protein. We studied one case of purely dermal spindle cell lipoma and four cases of classically subcutaneously located lesions arising in one female and four male patients (age ranged from 55 to 69 years). The neoplasms arose on the nose, the chin, the neck, the forehead, and retroauricular, and all lesions were marginally or incompletely excised. The analysed cases showed the classical histological and immunohistochemical features of spindle cell lipoma, but in addition, a strong expression of S-100 protein by spindled tumour cells was noted in all cases. Cases of S-100-positive spindle cell lipoma may cause problems in the differential diagnosis to neural and melanocytic neoplasm, and emphasize the plasticity of the spindled cells in spindle cell lipoma.

**Key Words:**        **Spindle cell lipoma**        **Lipoma**        **S-100 protein**

## **Introduction**

Spindle cell lipoma represents a distinct clinicopathological entity and forms a morphological spectrum with pleomorphic lipoma sharing clinical, histological, immunohistochemical and genetic features. Classical spindle cell lipoma usually presents as an asymptomatic, long-standing, mobile lesion in the subcutaneous tissue, and the majority of cases are seen on the posterior neck, shoulder, and upper back of elderly male patients. Infrequently, spindle cell lipoma arises in the oral cavity, the face and the extremities (1,2,3). In contrast purely dermal spindle cell lipoma shows a broad anatomic distribution and no gender preference (4). Very rarely cases of familial spindle cell lipoma with multiple lesions in the affected patients have been reported (5). Subcutaneously located spindle cell lipoma represents a well-circumscribed lesion composed of mature adipocytes and a variable number of bland spindle-shaped tumour cells set in a collagenous and myxoid stroma with hyalinised rope-like collagen fibers, blood vessels, and often mast cells are seen. The pseudoangiomatous variant, containing numerous-, slit-like spaces resembling vascular channels (6), and cases of spindle cell lipoma composed entirely of spindled tumour cells (7) may cause considerable problems in the differential diagnosis. Purely dermal spindle cell lipoma is poorly circumscribed and infiltrative mimicking a more aggressive neoplasm (4). Immunohistochemically, the tumour cells of spindle cell lipoma stain positively for CD34 (8), and show loss of retinoblastoma protein expression (9); very rarely, an expression of desmin by spindled tumour cells has been reported (10). We report five cases of spindle cell lipoma showing an expression of S-100 protein by spindle-shaped tumour cells, and discuss the problems in the differential diagnosis.

## **Materials and methods**

The cases were identified in the routine diagnostic files and in the consultation files of the authors. Clinical information was obtained from the laboratory request forms and contributing pathologists and clinicians. In each case, tissue was fixed in 4% buffered formalin, and routinely processed and embedded in paraffin; 4 µm thick sections were stained with haematoxylin and eosin. In addition, sections were stained immunohistochemically by the labelled Streptavidin Biotin (LSAB) technique using commercially available antibodies; antigen retrieval was used for all antibodies at pH 6.1 (HPCA-1, S-100 protein) as well as 9.0 (Rb-1, Sox10). The following antibodies have been used: S-100 protein (polyclonal, dilution: 1:2000, source: DAKO,

Heidelberg, Germany), CD34 (HPCA-1, 1:100, BD Biosciences, Heidelberg, Germany), and Rb-1 (G3-245, 1:100, BD Biosciences, Heidelberg, Germany). Three cases were stained for Sox10 as well (EP268, 1:200, MEDAC, Wedel, Germany). Appropriate positive and negative controls were used in each case.

## **Results**

The clinical features are summarized in Table 1. Briefly, the neoplasms were seen in four male and one female patient (age range from 55 to 69 years) and arose on the tip of the nose, the chin, the neck, the forehead, and retroauricular. The size of the lesions ranged from 0.6 cm to 2.5 cm and all lesions were marginally or incompletely excised. Case 1 represented a superficially ill-defined dermosubcutaneous lesion (Figure 1), whereas cases 2, 3, 4, and 5 arose in the subcutis as nodular, well-circumscribed, partly encapsulated neoplasm. All five cases were composed of mature adipocytes without prominent atypia and a variable number of cytologically bland spindled tumour cells. Only few spindled cells were noted in Case 2, whereas the spindle-shaped cells predominated in Case 3 (Figure 2). Neoplastic cells were set in a collagenous stroma in Case 3, prominent myxoid stromal changes with numerous blood vessels were noted in Case 3, prominent myxoid stromal changes with numerous blood vessels were noted in Cases 1, 4, and 5 (Figure 3). Immunohistochemically, spindle-shaped cells in all four cases stained positively for CD34 (Figure 4), and showed loss of retinoblastoma protein expression (Figure 5). Surprisingly, the spindled cells also expressed S-100 protein strongly with a nuclear and cytoplasmic positivity (Figure 6). All cases tested were negative for Sox10.

## **Discussion**

Spindle cell lipoma and pleomorphic lipoma represent a morphologic spectrum of a single clinicopathologic entity with shared molecular changes. It has been reported that many cases show monosomy and partial losses involving chromosomes 13 and 16 (11), and the majority of investigated cases is characterized by loss of retinoblastoma protein expression (9). Interestingly, the overlapping histological and molecular features between spindle cell lipoma, cellular angiofibroma and mammary-type myofibroblastoma raised the suggestion that these neoplasms represent points along a single spectrum of related lesions with morphological differences dependent on the anatomic location (12,13).

Given the broad morphological spectrum of spindle cell lipoma, ranging from cases with few CD34-positive spindled cells only to cases that are composed predominantly or even entirely of these spindled cells, the differential diagnosis includes a number of CD34-positive spindle cell mesenchymal neoplasms, such as perineurioma, dermatofibrosarcoma protuberans, and solitary fibrous tumour. Extraneural (soft tissue) perineurioma is composed of spindled cells that stain positively for CD34 in a considerable number of cases; however, the tumour cells in perineurioma contain elongated and very thin cytoplasmic processes and slender nuclei, they stain positively for perineurial markers (EMA, claudin-1, glut-1) and do not show a loss of the expression of retinoblastoma protein. Dermatofibrosarcoma protuberans is also composed of cytologically bland CD34-positive spindled cells; however, these neoplasms show a diffuse, honey-comb infiltration of the subcutaneous tissue and different genetic changes. Cases of solitary fibrous tumour may contain fat cells (so-called fat-forming solitary fibrous tumour), and tumour cells stain positively for CD34 as well. In contrast to spindle cell lipoma, solitary fibrous tumour is characterized by a varying cellularity, the presence of haemangiopericytoma-like blood vessels, and tumour cells show a nuclear expression of STAT6 due to characteristic genetic changes with *NAB2-STAT6* gene fusion (14).

The reported expression of S-100 protein by spindled cells in otherwise typical cases of dermal and subcutaneous spindle cell lipoma raises additional differential diagnoses. Neurofibroma, especially diffuse neurofibroma, is composed of bland spindle-shaped tumour cells staining positively for S-100 protein, and these neoplasms often contain numerous CD34-positive fibroblasts as well. However, examples of subcutaneously located spindle cell lipoma are usually encapsulated lesions and tumour cells show loss of retinoblastoma protein expression, and are Sox10 negative. In contrast neurofibroma shows an expression of Sox10, a transcription factor of the sex determining region Y (SRY)-related high mobility group (HMG)-box gene family that is expressed in melanocytes and Schwann cells (15). Cases of desmoplastic malignant melanoma are composed of S-100-positive spindled cells that may show a relatively bland cytomorphology; however, in a number of cases coexistent lentigo maligna is present, a focal lymphocytic infiltrate in the desmoplastic tumour stroma is evident, and neoplastic cells in desmoplastic malignant melanoma stain positively for

p75 and Sox10. Encapsulated schwannoma does not contain lipogenic cells, the neoplastic cells are larger with tapering nuclei and abundant eosinophilic cytoplasm, and there is a different vascular pattern with dilated vessels with fibrosed vessel walls. Other S-100-positive neoplasms that are easily distinguished morphologically include granular cell tumour, metastatic malignant melanoma and myoepithelioma.

The spindle cells in spindle cell lipoma are bland, immature, non-fat storing mesenchymal cells that show a variable immunophenotype. In addition to the expression of vimentin and CD34 these cells may stain positively for desmin and S-100 protein as well, and it has been suggested that spindle cell lipoma may “arise” from immature mesenchymal cells capable of different lines of differentiation (16).

In summary, we report four cases of otherwise typical spindle cell lipomas arising in the subcutis or in the dermis that showed an expression of S-100 protein by spindled tumour cells, what represents a potential diagnostic pitfall and has to be considered in the differential diagnosis of S-100-positive spindle cell neoplasms of skin and subcutis.

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**Table 1: Clinical features of four cases of S-100 positive spindle cell lipoma**

Case no	Age (years)	Gender	Location	Size (cm)
1	69	F	Nose	0.6
2	59	M	Chin	1.5
3	69	M	Neck	2.4
4	55	M	Forehead	2.5
5	59	M	Retroauricular	1.3

## **Figure Legends:**

**Figure 1:** An ill-defined dermal lesion composed of mature lipogenic cells and spindle-shaped tumour cells is seen in Case 1.

**Figure 2:** Numerous bland spindled cells associated with adipocytes are set in a collagenous stroma with hyalinised collagen fibers in Case 3.

**Figure 3:** Prominent myxoid stromal changes are noted in Case 5

**Figure 4:** Spindle-shaped tumour cells in all cases stained positively for CD34.

**Figure 5:** Most tumour cells showed loss of retinoblastoma protein expression.

**Figure 6:** Spindled tumour cells showed an expression of S-100 protein as well.